Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 3 Issue 5 May 2019

Review article

The Status of Elemental Impurities Over a Decade: A Review

Manthan Trivedi, Margi Gandhi and Rajashree Mashru*

Faculty of Pharmacy, The M.S. University of Baroda, India

***Corresponding Author:** Rajashree Mashru, Faculty of Pharmacy, The M.S. University of Baroda, India.

Received: March 01, 2019; **Published:** April 23, 2019

Abstract

The presence of elemental impurities in the pharmaceutical products is needed to be analysed and has been done for many decades. Over the past decade (2009 - 2018) significant progress has been made in this field from using special reagents which form precipitate with the metallic impurities and are detected by colorimetric methods to using highly sensitive and selective methods of analysis such as Flame Photometry, Flame - Atomic Absorption Spectroscopy (F-AAS), Graphite Furnace - AAS, Cold-Vapour - AAS, Inductively Coupled Plasma - Mass Spectroscopy (ICP-MS), X-ray Fluorescence Spectrometry (XRF) and Laser Ablation - ICP -MS (LA-ICP-MS) for which a brief account has presented herein.

Keywords: Elemental; Impurities; Limits; USP <231 - 233>; Flame Photometry; AAS; ICP-MS; XRF; LA-ICP-MS

Introduction

Many different types of elemental impurities may be present in the pharmaceutical products including certain metals, catalysts, environmental contaminants and excipients [1]. These impurities may come from natural sources, equipment which are used in the synthetic methods, closures or may be added intentionally by the manufacturer of the product. When elemental impurities are known to be present, have been added, or have the potential for introduction, assurance of compliance to the specified levels is required. Thus, a risk based control strategy would be beneficial to the analyst to assure the compliance of these limits with the standard values.

Arsenic, Cadmium, Lead, Mercury must be assessed in risk assessment in all products. The detection and control of these impurities becomes essential because they provide no therapeutic benefit and also may exert toxic effects to the patients.

Detection of elemental impurities according to Indian Pharmacopoeia [2]

The different editions of the Indian Pharmacopoeia up to 2018 have shown the use of experiments in which the determination of those metallic impurities in the official substances are done based on their ability to form coloured complexes with specific reagents under test conditions. These coloured solutions are then compared with the standard comparison solution and are ex-pressed as a part of lead per million parts of the substance under examination.

Experiment for heavy metals

Solution A: Introduce into a 50 ml Nessler tube 2 ml of dilute acetic acid Sp. and exactly the quantity of standard lead solution containing the lead equivalent of the heavy metals limit specified for the sub-stance to be tested and make up the volume up to 25 ml with water.

Solution B: This consists of 25ml of the solution prepared for this test according to the specific directions in the individual monograph.

Procedure: Transfer solutions A and B to matching 50 ml Nessler tubes, add 10 ml of Hydrogen sulphide to each tube, mix allow to stand for 10 minutes, then view downwards on a white surface the colour of the solution B is no darker than that of solution A.

Over the years there has been a transition from the use of limit tests and heavy metal tests for the determination of the presence of these elemental impurities to a modern approach using sophisticated instrumental techniques.

Detection of elemental impurities according to the United States Pharmacopoeia [3]

Up until 2009 the United States Pharmacopoeia also stated the use of colorimetric methods in which the test solutions are visually

compared with a control pre-pared from a standard lead solution. These tests were provided to make sure that the content of metallic impurities which are coloured by sulphide ion do not exceed the heavy metal limits specified in the individual monographs.

Under the USP chapter <231> special reagents are listed which are used in these colorimetric techniques such as Lead nitrate stock solution, Acetate buffer (pH 3.5) and Standard lead solution.

The tests given under this chapter will be able to detect the following metals: Pb, Hg, Bi, As, Sb, Sn, Cd, Ag, Cu, and Mo.

Colorimetric method [3]

Standard preparation: Into a 50 ml colour comparison tube pipet 2 ml of Standard Lead Solution (20 µg of Pb) and dilute with water to 25 ml. Using a pH meter or short range pH indicator as external indicator, adjust with 1N acetic acid or 6N ammonium hydroxide to a pH between 3.0 and 4.0, dilute with water to 40ml and mix.

Test preparation: Into a 50ml colour comparison tube place 25ml of the solution pre-pared for the test as directed in the individual monograph. Using a pH meter or short range pH indicator as external indicator, adjust with 1N acetic acid or 6N ammonium hydroxide to a pH between 3.0 and 4.0, dilute with water to 40 ml and mix. (This is for those substances that yield clear colourless preparations under the specified conditions. Other methods are given for coloured preparations and volatile oils.)

Control/monitor preparation: Into a third 50 ml colour comparison tube place 25ml of a solution prepared as directed for test preparation, add 2 ml of Standard Lead Solution. Using a pH meter or short range pH indicator as external indicator, adjust with 1N acetic acid or 6N ammonium hydroxide to a pH between 3.0 and 4.0, dilute with water to 40 ml and mix.

Procedure: To each of the three tubes add 2 ml of pH 3.5 Acetate Buffer, then add 1.2 ml of thioacetamide-glycerin base TS, dilute with water to 50 ml, mix and allow to stand for 2 minutes. View downwards over a white surface: The colour of the Test Preparation is not darker than the Standard preparation, and the colour of the Monitor Preparation is equal to or darker than that of the solution from the Standard Preparation.

The <231> chapter of the USP was only official until January 1st, 2018. This chapter has now been replaced with new chapters which include:

- USP <232>: ELEMENTAL IM-PURITIES - LIMITS
- USP <233>: ELEMENTAL IM-PURITIES - PROCEDURES
- USP <2232>: ELEMENTAL CONTAMINANTS IN DIETARY SUPPLEMENTS

Table 1 [1] represents the permitted concentration of the elemental impurities as per the USP 2018.

Element	Oral Concentration (µg/g)	Parenteral Concentration (µg/g)	Inhalation Concentration (µg/g)
Cadmium	0.5	0.2	0.2
Lead	0.5	0.5	0.5
Arsenic	1.5	1.5	0.2
Mercury	3	0.3	0.1
Cobalt	5	0.5	0.3
Vanadium	10	1	0.1
Nickel	20	2	0.5
Thallium	0.8	0.8	0.8
Gold	10	10	0.1
Palladium	10	1	0.1
Iridium	10	1	0.1
Osmium	10	1	0.1
Rhodium	10	1	0.1
Ruthenium	10	1	0.1
Selenium	15	8	13
Silver	15	1	0.7
Platinum	10	1	0.1
Lithium	55	25	2.5
Antimony	120	9	2
Barium	140	70	30
Molybdenum	300	150	1
Copper	300	30	3
Tin	600	60	6
Chromium	1100	110	0.3

Table 1: Permitted concentrations of elemental impurities for individual component option [1].

It was in the year 2010 when the International Conference on Harmonisation (ICH) published the "Guidelines for Elemental Impurities (Q3D)" which pro-vided a globally accepted limit to the presence of metallic impurities in the drug products given in table 2 [4]. Table 3 [5] shows the concentration of impurities per-mitted in the various excipients present in the drug formulation.

Element	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalation (µg/day)
Antimony (Sb)	1200	94	22
Arsenic (As)	15	15	1.9
Barium (Ba)	1460	730	343
Cadmium (Cd)	5	1.7	1.7
Chromium (Cr)	10700	1070	2.9
Cobalt (Co)	50	5	2.9
Copper (Cu)	3400	340	347
Gold (Au)	134	134	1.3
Lead (Pb)	5	5	5
Lithium (Li)	560	280	25
Mercury (Hg)	30	3	1.2
Molybdenum (Mo)	3400	1700	11
Nickel (Ni)	220	22	6
Palladium (Pd)	100	10	1
Platinum (Pt)	108	10.8	1.4
Selenium (Se)	170	85	135
Silver (Ag)	167	14	7
Thallium (Tl)	8	8	8
Tin (Sn)	6400	640	64
Vanadium (V)	120	12	1.2

Table 2: PDE of certain metals through the different routes of administration [4].

Component	Maximum Permitted Concentrations (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	0.5	1.5	0.5	3	10	10	20
MCC	0.5	1.5	0.5	3	10	10	20
Lactose	0.5	1.5	0.5	3	10	10	20
Ca Phosphate	0.5	1.5	0.5	3	10	10	20
Crospovidone	0.5	1.5	0.5	3	10	10	20
Mg Stearate	0.5	1.5	0.5	3	10	10	20
HPMC	0.5	1.5	0.5	3	10	10	20
Titanium Dioxide	0.5	1.5	0.5	3	10	10	20
Iron Oxide	0.5	1.5	0.5	3	10	10	20
Maximum Daily Intake (µg)	1.25	3.75	1.25	7.5	25	25	50
PDE (µg)	5	15	5	30	100	100	200

Table 3: Permitted concentrations for various excipients used in the pharmaceutical product (Assuming uniform concentrations and 10g daily intake) [5].

Classification of the elemental impurities according to ICH [6]

The elemental impurities may be classified into three classes based on their toxicity and the reasonable probability of their presence in the drug products. The probability that a metal impurity would be present in the drug product is dependent on the equipment used in the pharmaceutical process, as well as the natural abundance and environmental distribution of the element.

Class 1: Human toxicants that have no use or limited use in the manufacturing of the pharmaceutical products. They require evaluation during risk assessment across all the potential sources of elemental impurities and route of administration because of their detrimental effect on humans.

Elements included: Arsenic (As), Cadmium (Cd), Mercury (Hg), and Lead (Pb).

Class 2: The elements included in this class are generally regarded as route-dependent human toxicants. They are further divided into two classes based on their likelihood of occurrence in the pharmaceutical product.

Class 2A: Elements have a high probability of occurrence in the drug product and hence are required to be assessed across all the potential sources and routes of administration.

Elements included: Cobalt (Co), Nickel (Ni), and Vanadium (V).

Class 2B: Elements have a reduced probability of occurrence in the drug product due to their low abundance and as a result they may be excluded from the risk assessment unless they are intentionally add-ed during the manufacture of the drug substance, excipients, or other components of the drug product.

Elements included: Silver (Ag), Gold (Au), Iridium (Ir), Osmium (Os), Palladium (Pd), Platinum (Pt), Rhodium (Rh), Ruthenium (Ru), Selenium (Se), and Thallium (Tl).

Class 3: The elements included in this class have a low toxicity by the oral route of administration (High PDE of about 5 00 µg/day) but may require consideration in the risk assessment for inhalation and parenteral routes of administration. For the oral route of administration unless these elements are intentionally added they do not need to be considered for risk assessment.

Elements included: Barium (Ba), Chromium (Cr), Copper (Cu), Lithium (Li), Molybdenum (Mo), Antimony (Sb), and Tin (Sn)

Other elements: Some elemental impurities have very low inherent toxicities and so if these elemental impurities are present or included in the drug product they are addressed by the as tests for particular elements. (e.g. presence of Al for compromised renal function, or Mn and Zn for patients with compromised hepatic function).

Elements included: Aluminium (Al), Boron (B), Calcium (Ca), Iron (Fe), Potassium (K), Magnesium (Mg), Manganese (Mn), Sodium (Na), Tungsten (W), and Zinc (Zn).

Chapter <233> of the USP de-scribes the advanced analytical procedures for the evaluation of the levels of the elemental impurities [7]. It also consists of the validation studies through which the

Chapter <233> of the USP de-scribes the advanced analytical procedures for the evaluation of the levels of the elemental impurities [7]. It also consists of the validation studies through which the analysts will confirm that the analytical procedures described are suitable for use on the specified material. The major instrumental techniques used now-a-days in the elemental analysis of impurities include the following:

1. Flame Photometry
2. Atomic Absorption Spectroscopy
3. Inductively Coupled Plasma - Mass Spectrometry
4. X-Ray Florescence Spectroscopy
5. Laser Ablation - ICP - MS

Flame photometry [7]

Flame photometry is an emission technique in which there is a linear correlation between the intensity and the concentration. Here the atoms are excited in a flame and the intensity of the emitted light is measured. It was in the early years that Flame photometry was used for the detection of all the metals. However, the exciting efficiency of the flames was poor which resulted in the high detection limits. Now-a-days this technique is restricted to only the alkali metals especially Na and K which are highly sensitive to this method. Table 4 [8] enlists the elements along with the emission wavelengths and the flame colour they would show under the flame.

Element	Emitted Wavelength	Flame Colour
Potassium (K)	766 nm	Violet
Lithium (Li)	670 nm	Red
Calcium (Ca)	622 nm	Orange
Sodium (Na)	589 nm	Yellow
Barium (Ba)	554 nm	Lime green

Table 4: Elements analysed by flame photometry [8].

Atomic absorption spectroscopy [9]

This method of elemental analysis uses samples in liquid or solid form. Here the application of electromagnetic radiation of specific wavelength from the source is done which will be absorbed by the different elements. Each element will absorb the electromagnetic radiation differently and hence by comparing these absorptions with that of the standard we may detect the element. Different types of Atomic Absorption Spectroscopy include:

1. Flame - Atomic Absorption Spectroscopy (F-AAS)
2. Graphite Furnace Atomic Absorption Spectroscopy (GF-AAS)
3. Cold-vapour Atomic Absorption Spectroscopy

Figure 1

ICP-MS [10]

Inductively Coupled Plasma - Mass Spectroscopy (ICP-MS) is a very advanced instrumental technique which is used in the elemental analysis of metals as well as several non-metals also.

Method

- **Standardization solution 1:** 1.5/ of the Target element(s) in a Matched Matrix.
- **Standardization solution 2:** 0.5/ of the Target element(s) in a Matched Matrix.
- **Sample stock solution:** The various forms of sample preparation include:
  - **Neat:** Used for liquids or alternative procedures that allow the examination of the unsolvated samples
  - **Direct aqueous solution:** Used when the sample is soluble in an aqueous solvent
  - **Direct organic solution:** Used when the sample is soluble in an organic solvent
  - **Indirect solution:** Used when a material is not directly soluble in aqueous or organic solvents. Total metal extraction is the preferred sample

preparation approach to obtain an indirect solution. Digest the sample using the closed vessel digestion procedure. The sample preparation scheme should yield sufficient sample to allow quantification of each element at the limit specified in the corresponding monograph.

- **Sample solution:** Dilute the Sample stock solution with an appropriate solvent to obtain a final concentration of the target element at NMT 1.5.
- **Blank:** Matched Matrix.
- **Mode:** ICP (Inductively Coupled Plasma).
- **Detector:** Mass spectrometer (Positive ions of stable isotopes).
- **Rinse:** Diluent is used
- **Typical detection limits:** Parts per billion in solution.

Figure 2

The above figure [11] depicts the various detection limits of elements which may be analysed using ICP-MS.

X-ray florescence spectroscopy [9]

X-Ray Florescence is a non-destructive technique which involves the irradiation of the sample with high energy excitation X-rays and the subsequent measurement of the emitted florescence from the sample at a fixed wavelength. There are three types of XRF used which include Wavelength dispersive XRF, Energy dispersive XRF and Total reflection XRF. Due to the high detection limits these techniques are not very popular for the quantitative determination of the metal impurities in the pharmaceutical samples.

Laser ablation-ICP-MS [9]

Laser ablation as the name suggests in the process of generating vapour from a solid surface when it comes in contact with a laser beam, this vapour is then subjected to ICP-MS. Laser ablation -ICP-MS is a rapid and powerful technique which is used for the multi-element detection. One major drawback to this technique is the lack of reference materials for the validation and calibration purposes.

Conclusion

Over the past decade it is seen that elemental impurities have been analysed using more sophisticated methods instead of the conventional colorimetric techniques. Before 2009 there was no standard limit for the presence of the elemental impurities present in the pharmaceutical formulations. Following the ICH Q3D guidelines standard limits became worldwide for the elemental impurities. It has been seen that during this decade up to January 2018 as the advanced techniques for the analysis of the elemental impurities (Flame photometry, AAS, ICP-MS, XRF, and Laser ablation) have become more selective and sensitive the limits of the same have be-come more and more stringent.

Bibliography

1. United States Pharmacopoeia, USP 41 NF 36, Volume 4 <232> Elemental Impurities - Limits: 6147-6151 (2018).
2. The Pharmacopoeia of India 1975 Supplement, Appendix-XXXVII, Heavy metal Test: 889-890 (1975).
3. United States Pharmacopoeia, USP 41 NF 36, Volume 4 <231> Heavy Metals: 6145-6147 (2018).
4. International Conference on Harmonisation, ICH Harmonised Guideline, Guideline for Elemental Impurities (Q3D), Individual Safety assessment: 23-67 (2014).
5. International Conference on Harmonisation, ICH Harmonised Guideline, Guideline for Elemental Impurities (Q3D), Table A.4.2 (2014): 68.
6. International Conference on Harmonisation, ICH Harmonised Guideline, Guideline for Elemental Impurities (Q3D), Elemental Classification: 4 (2014).
7. Flame Photometry. Science Direct.
8. Flame Photometer: Principle, Components, Working Procedure, Applications, Advantages and Disadvantages (2017).
9. V Balaram. "Recent advances in the determination of elemental impurities in pharmaceuticals -Status, challenges and moving frontiers".
10. United States Pharmacopoeia, USP 41 NF 36, Volume 4 <233> Elemental Impurities - Procedures: 6151-6155 (2018).
11. What is ICP-MS?... and more importantly, what can it do?

Volume 3 Issue 5 May 2019